The Future Independence and Progress of American Medicine in the Age of Chemistry

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A REPORT

BY

JOHN J. ABEL
CARL L. ALSBERG
RAYMOND F. BACON
F. R. ELDRED
REID HUNT
TREAT B. JOHNSON
JULIUS STIEGLITZ
F. O. TAYLOR
CHARLES H. HERTY, *Chairman*

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WE ask the careful reading, discussion and consideration of this report by physicians and surgeons, by mothers and fathers, by educators, hospital directors and trustees and all others whose hearts are interested in the welfare of the future generations of American children.

FOREWORD

This report is the outgrowth of an editorial which appeared in the Journal of Industrial and Engineering Chemistry (September, 1918), pointing out the need for intensive chemical research, under more favorable conditions than exist today, devoted to the alleviation of human suffering. The ensuing discussion led to the appointment of a committee of the American Chemical Society in January, 1919, to prepare a statement of plans and policies for the facilitation of research in this field. Since that date this committee has held frequent meetings, and has had the coöperation and advice of leaders in the several sciences which bear upon this problem.

In order that the views of the committee and the facts upon which they are based should be made available for the thoughtful people of this country, The Chemical Foundation, Inc., arranged for the preparation of a comprehensive report on this subject.

The report has been drafted by the following Sub-Committee: Julius Stieglitz, Reid Hunt, Treat B. Johnson, F. R. Eldred and Charles H. Herty, Chairman.

This report has received the unanimous approval of the following committee:

John J. Abel

Professor of Pharmacology, Johns Hopkins Medical School, Baltimore, Md.
Editor, Journal Pharmacology and Experimental Therapeutics

Carl L. Alsberg

Director, Food Research Institute, Stanford University, Cal.
Formerly Chief of the Bureau of Chemistry, Department of Agriculture
Member, Council of Pharmacy and Chemistry, American Medical Association

Raymond F. Bacon

Director, Mellon Institute for Industrial Research, Pittsburgh, Pa.

F. R. Eldred

Chemical Consultant, Eli Lilly & Co., Indianapolis, Ind.

Reid Hunt

Professor of Pharmacology, Harvard Medical School, Boston, Mass.
Formerly of U. S. Public Health Service
President, U. S. Pharmacopœia Convention

Treat B. Johnson

Professor of Organic Chemistry, Yale University, New Haven, Conn.

Julius Stieglitz

Chairman, Department of Chemistry, University of Chicago, Chicago, Ill.
Past President, American Chemical Society
Chairman, Subcommittee on Synthetic Drugs, National Research Council
Vice-Chairman, Council of Chemistry and Pharmacy, American Medical Association

F. O. Taylor

Chief Chemist, Parke, Davis & Co., Detroit, Mich.

Charles H. Herty, *Chairman*

Editor, Journal of Industrial and Engineering Chemistry, New York City
Past President, American Chemical Society.

INTRODUCTION

Research for the Late War.—When it became clear during the recent war that poisonous gas was to constitute an important munition, our country called to its service a great group of its ablest research chemists to provide efficient means of defense and to solve those problems of production which would provide our field forces with an ample supply of this new weapon.

Not to the professional inventor nor to the accident of haphazard discovery was this grave responsibility assigned, but to the trained workers in systematic research. Nor were these men asked to undertake this vital work in the seclusion and isolation of their respective laboratories but they were assembled at the American University Experiment Station on the outskirts of the city of Washington, under one roof as it were, where by daily, nay hourly, conference utmost speed could be secured in the solution of those problems on which the question of life and death so closely hung.

But these chemists found that they alone were inadequate for the task. To supplement their special skill and knowledge there were added to the staff pharmacologists and experimental pathologists.

Through the combined efforts of these groups, working in closest association and provided with ample facilities for research, results were accomplished with a speed and certainty which amazed all. The paths to agencies for both defense and offense

were clearly pointed out and large scale production quickly followed.

The Battle Against Disease.—Is there no valuable lesson for peace in this mighty and successful effort in the making of war? Is there not another battle constantly to be fought—the battle against disease? While war claims its sacrifice in millions of lives, disease each year claims its tens of millions. Pneumonia, influenza, tuberculosis, cancer, meningitis, malaria, epilepsy, insanity, feeble-mindedness, malnutrition, abnormal development, and a multitude of other diseases claim their many victims. And what a host of wounded do we have in this destructive war of peace—men, women and children who suffer, often longing for death as a relief, their efficiency crippled and their future on earth beclouded!

Can we not bring to these problems the same methods so successfully employed in the solution of means of making war? The experience of the ages is now being drawn upon in this fight against disease, but the means are entirely inadequate as shown by the continued ravishment of disease. Too often, in default of exact knowledge, we blindly seek remedial agencies. The annual drug bill of this nation is in round numbers $500,000,000, of which amount $300,000,000 is spent for so-called patent medicines. The number of medicaments is increasing at a tremendous rate, beyond all proportion to the amount of systematic research being devoted to the subject. Thirty years ago 2,699 drug items were reported to be on the market; today more than 45,000 are said to be in use. The frailties and suffering of humanity are being grossly exploited.

Medicine and Chemistry.—Several centuries ago the chemist and the physician coöperated closely for

the alleviation of suffering; the chief aim of chemistry in those days was the providing of medicinals for the use of the physician. Then the physician and the chemist separated, the physician looking more and more to other means to effect his ends, while the chemist turned to the production of wealth in the industries, as illustrated by the pioneer work of Agricola on metallurgy, a work recently translated and edited by Mr. and Mrs. Herbert Hoover. Later the physician turned back somewhat to his former aid and found most useful substances awaiting him. For instance, ether had been discovered in the thirteenth century, but its value as an anæsthetic was not definitely recognized until 1846. During the intervening five or six hundred years untold suffering resulted from lack of knowledge of its application in producing insensitiveness to pain. Magnesium sulphate was well known to chemists in 1694, but two hundred years elapsed before it was learned what great relief it gave in lockjaw, burns, and strychnine poisoning. Twenty-three years elapsed between the discovery of amyl nitrite by the chemist and the discovery of its medicinal properties by the physician; during this period tens of thousands of human beings suffered the tortures of angina pectoris because the chemist, pharmacologist and physician were not working together.

The Human Chemical Factory.—There has been a return to the earlier views as to the relation of chemistry to medicine. Each human body is now recognized to be a chemical factory in which the most complicated chemical and physical changes are continuously taking place. When these reactions are normal from day to day, we are in good health. When they are abnormal, they are a direct cause of disease, as in gout, diabetes, goiter, and other serious

diseases. Moreover, when abnormal, these fundamental chemical reactions lower the natural resistance of the body, especially to invading disease germs, and they thus lead indirectly to infection, disease and death. Thus, it is well known that the chief danger to the diabetic patient under proper medical care is found in his abnormally low resistance to infection as the result of the inability of the body to maintain its normal chemical reserve. Even the invading disease germs in most cases carry out their fell work through chemical agencies, through the production of potent poisons (toxins) acting on the heart, the respiratory nerve centers, or some other vital organ, or gradually poisoning the whole system.

Chemistry Must Solve Problems.—The bacteriologist and pathologist have accomplished wonders in the present and the last generations in tracing the living carriers of the great infectious diseases, and the world owes our Pasteurs, Kochs, Behrings, Flexners and many other valiant workers with these deadly carriers of disease a debt of eternal gratitude. But the fact is that bacteriologist and pathologist have now definitely reached the point where they must turn to chemistry for the solution of many of their most important problems. As an illustration: their antitoxins, their most powerful weapons in combating invading germs, are chemical substances of specific curative power but of unknown composition and never isolated as yet as pure principles. They are always injected into our bodies in the form of crude mixtures, loaded down with undesirable and to some extent even harmful ingredients. The isolation of the pure principles by chemical methods, supplementing the pioneer work of bacteriologist and pathologist, would prove one of the

greatest advances in medicine, giving the practitioner the power to combat an infection by swift, exact and sufficiently powerful doses, where now he often acts with hesitation and misgiving. Another instance: coöperation of the medical investigator with the chemist (Dr. John Howland and his collaborators) has recently led to the recognition of the fact that in rickets, the scourge of many thousands of children, there is a deficiency of such common chemical components as lime and phosphate in the blood—a discovery that by the same coöperation must ultimately lead to successful preventive methods. But how long must the thousands of little victims wait for relief?

In the ultimate cell itself, in the protoplasm of that cell, chemical reactions take place which in a fundamental way determine health or sickness—and of these reactions we know but little.

The Chemist's Aid.—How can chemistry, coöperating now with medicine as it coöperated with the war and naval departments, help best in this battle against disease?

First—The chemist is being called upon for the preparation of specific medicaments for the cure or alleviation of specific diseases. Salvarsan ("606"), the product of chemical research in coöperation with medicine, has done more in four years for the elimination of syphilis than was accomplished in four centuries of hygiene and education. So, too, the naturally occurring cocaine, so valuable as a local anæsthetic and yet so often poisonous, has, by careful chemical study, been found to be a very complex chemical compound, to only certain parts of which was to be ascribed its beneficent anæsthetic effect, other parts carrying useless poisonous qualities of no value to man. Thus was the chemist enabled to

improve on nature, and there resulted procaine, better than cocaine because equally good as an anæsthetic and yet without secondary poisonous characteristics. Today a modification of quinine gives promise as a specific cure of pneumonia; it destroys the pneumococcus germs in glass vessels, but it is still too poisonous to be used in sufficient strength to combat the hosts of invading germs in the human body stricken with pneumonia.

Field Rich in Promise.—So, too, the study of the pure principles of our organs of secretion opens up a field rich in promise. The isolation and study of epinephrine (adrenalin) has furnished a means of relieving the intense suffering of acute bronchial asthma, of checking hemorrhage and, used under proper conditions, of carrying the strained heart through the shock of operation, the critical stages of pneumonia. The isolation of the active principle of glands controlling normal growth, of those of digestion and metabolism, of antitoxins, vaccines, serums, etc., as mentioned above, all await the hands of the chemist and when isolated and prepared pure will place in the hands of physicians material which can be administered with absolute accuracy and which gives promise of instantaneous effect by hypodermic injection.

Second—Life is dynamic, not static; and so the physical chemist must be called into active participation in this work. The matter of health is closely bound up in the delicate adjustment of speed of the various chemical reactions taking place in the body. These reactions may be accelerated or retarded by minute quantities of catalyzers (enzymes, such as pepsin). So, too, the brilliant advances by physical chemists in the study of colloids have found as yet but imperfect application to the problems of the

body, where in nerve and cell, muscles and organs, the questions to be dealt with are largely those of colloidal chemistry.

Coöperating Sciences.—These complex problems of the body are too infinitely complicated to be solved by any one class of scientists. Preëminently chemical in their nature, the chemist alone is imperfectly equipped to carry them to complete and successful solution. He must join hands with the pharmacologist, the pathologist and the experimental biologist. For that reason much of the work in progress today is halting and uncertain. In a few institutions such coöperation is had, though too often the chemist plays the minor rôle. In our universities constant work is in progress and should be generously supported, but too often the workers are isolated and with only part time to devote to research because of the claims of teaching duties. Too often the chemist needs the knowledge and technique of the biologist, and equally often the biologist needs the chemist's information and point of view. But the lesson of the war is before us and we know what great results may be expected of *coöperation under ideal conditions of time and equipment for research.* Is not the battle against disease much more imperative in its call than the battle of man against man?

Outlet for Practical Idealism.—But the latter war was carried out under government control, and since all are subject to disease it may be argued that the prosecution of similar work in times of peace should be a government undertaking, just as fire control is a common tax upon the inhabitants of a municipality. It has been contrary, however, to the practice of our legislators to provide means for carrying on fundamental scientific research in government laboratories. Such laboratories exist for

the enforcement of laws or for other utilitarian purposes rather than for the prosecution of fundamental research. In peace the desire is to get away from government control.

Nor can the manufacturers of drugs be looked to for the carrying out of any such undertaking. The results of this work will doubtless be the elimination of many ineffective drugs now manufactured, while for those which persist the actual amounts to be manufactured are too small to attract capital to its support.

If such work is to be successfully prosecuted in our midst, it must be through the practical idealism of America, which can here find abundant outlet in providing such conditions as will direct the future energies of chemistry in America to this greatest blessing to mankind, a blessing which will not be confined to its own borders, but which will stretch out its helping hands to all suffering humanity.

THE RELATION OF THE FUNDAMENTAL SCIENCES TO MEDICINE

Chemistry and Physics and Life.—Chemistry is the fundamental science of the transformation of matter. Physics is the fundamental science of the transformation of energy or power to do work. Life in all of its forms, from its beginning to its end, is the highest, most complex expression of the transformation of matter and of the transformation of energy. In these direct statements—which will be presently elucidated by being considered from various points of view—we have the key to the trend of the most important phases of modern medical research, to the faith of a large group of scientific men in its future.

Need for Concerted Attack.—It is a fact daily becoming more impressive, that medicine by the very force of the fundamental nature of life in its material aspects, is turning more and more to chemistry and to physics for the final solution of many mighty and perplexing problems of the prevention and cure of disease. Thus the great British physiologist Bayliss says in the Introduction to General Physiology (1919): "As physiologists, our task is to refer, as far as we can, all phenomena of life to the laws of physics and chemistry." By the same token, there is no undertaking which could hold out greater promise of positive and far-reaching results in almost every branch of medicine

than *concerted* attack upon its problems by the close coöperation of expert chemists, expert physicists, expert biologists and medical men organized on the basis of this fundamental point of view: that life is the most complex expression of the transformation of matter and energy and that chemistry and physics are the fundamental sciences of the transformation of matter and energy. There is at present in this country no research center organized for such an attack by closest coöperation *under the leadership of these fundamental sciences.* The urgent need for such an organization should become apparent from a more detailed consideration of the propositions just now laid down.

Medicine is concerned with the preservation of life and we will first examine in a brief survey the problem of life from its material side, which forms the foundation of medical science. We will then consider, again briefly, what chemistry, and to a certain extent physics, are chiefly concerned with, and we will thus be prepared finally to turn to the main part of our study, the consideration of the specific ways in which the fundamental sciences are needed to serve the science of medicine, the consideration of some of the great specific problems which chemistry and physics must solve for medicine.

I. *Living Organisms Are Chemical Laboratories*

Life Is Chemical Activity.—What justification have we for the sweeping assertion that life in all its forms, be it vegetable, animal or human, is the highest expression of the transformation of matter and of energy? When we plant seeds in the fertile soil, the first stage of development consists in the transformation with the aid of water of the food,

starches, proteins, fats, stored in the seed itself, into rootlets, striking down into the soil below, and into stem and stalk, striking upward to reach finally the free air above. From the soil the rootlets absorb water and mineral salts—potash, lime, sulphates, phosphates, nitrogen in the form of nitrates and ammonia; from the air above the growing plant absorbs and transforms with the aid of the energy of sunlight carbon dioxide, the waste product of all animal life and of our cities' furnaces. From these simple ingredients thus taken from soil and air, the plant manufactures an infinite variety of new chemical substances, including carbohydrates (starches, sugars, gums, cellulose, wood), proteins, fats and oils, alkaloids (quinine, strychnine, morphine), dyes, and innumerable other substances. We have here in our growing plants tremendously intensive and infinitely varied *chemical laboratories,* on the output of which all animal life and in particular all human life is finally dependent for its very existence.

Chemists Help Agriculturists.—It is well known that the careful guidance of the chemist in the study of the soil, in the providing of proper food for the plant in the form of fertilizers, nitrates, ammonia, potash, phosphates—has made it possible to multiply the yield of our acres at small cost by intensive cultivation; but this is only a small fraction of what the chemist has done, is doing and will do in raising agriculture and forestry, with the aid of the expert botanist, from arts to the level of exact sciences—with untold benefit to mankind.

Biology Calls Chemical Aid.—Human life, like all animal life, quite obviously, is also dependent in its every instant on the chemical transformation of matter; from our inception to our return to dust,

we are transforming carbohydrates, fats, proteins, salts, water; every breath we draw, every motion we make involves chemical combustion. The assimilation of our food, its proper utilization, its proper elimination, every single function indeed of our life is dependent on definite chemical and physical processes. No wonder, indeed, is it that ultimately it is the chemist and the physicist who are called to his assistance by the watchful guardian of these complex chemical laboratories, the medical practitioner, in the search for the final exact knowledge for the proper control of the healthy functioning of life. Indeed, so profound are these relations that even the ultimate questions of life, of paramount moment to the race, the fertilization of the seed, the enlivening of the ovum—so like the kindling of a flame—the problems of heredity, of transmission of race and character from generation to generation—all these great questions are being recognized as fundamental problems for whose answer biology has at length called in the aid of chemistry.

Chemistry Underlies Medical Service.—It is not surprising—as pointed evidences of the modern trend—that leading medical schools are increasing two and three fold the preparation in these fundamental sciences and especially in chemistry, demanded of students for admission to their classes; it is not surprising that pioneer medical men, engaged in research, are returning in numbers to our universities to study more and still more chemistry and physics as they find them absolutely essential to the proper development of their investigations. There is no more overloaded student than the medical student of today, there is no more taxed professional man than the success-

ful physician—and if these men, in the face of extreme demands on their time and strength, devote ever more of this precious time to the study of the fundamental sciences of chemistry and physics, there must indeed be an urgent, compelling force—and that is simply the ever-increasing recognition of the fact that life has its abode in a highly complex laboratory controlled by chemistry and physics.

Ancient Connection of Medicine and Chemistry.—In this trend of recent years it is of interest to note that we are but returning to the earliest consciousness of the intimate relations between chemistry and medicine. Indeed, the very name chemistry refers to the land of Chêmi (Egypt) where chemistry originated in the temples in which priests experimented with simple chemicals for the preparation of medicinals. For many centuries indeed the connection between medicine and its daughter science chemistry was so close that in the sixteenth century the great physician and chemist Paracelsus stated that "the true purpose of chemistry is not to make gold, but to prepare medicines." How fruitful this conception was in the hands of Paracelsus is shown by the fact that he introduced into medicine the use of mercury, lead, sulphur, iron, arsenic, copper sulphate, laudanum—some of the drugs most valued at the present day. But in spite of this valiant protest of Paracelsus, chemistry drifted away from medicine, first in the effort to make gold by the conversion of baser metals, later in the much more successful efforts to create riches by the application of chemistry to industrial processes, for most of our great modern industries, from the making of steel and iron to the manufacture of dyes, are, indeed, in largest measure based on chemical processes. It is noteworthy, too, that the com-

paratively recent return of chemistry to the service of medicine was signalized at the outset by Chemistry's gift to Medicine of Pasteur, one of the great founders of modern medicine and one of the greatest benefactors of the human race.

II. *How Chemistry Attacks Its Great Problems*

If we turn now to the consideration of what chemistry is occupied with, its rôle of the fundamental science of the transformation of matter, we will more clearly perceive exactly how it can and must serve as the handmaiden of medicine. In their efforts to understand, indeed to master the transformation of matter, chemists have followed two great lines of attack; in both of these chemistry has aimed to be an absolutely *exact science*, as exact, indeed, as mathematics—so that it may attain its objects with the accuracy and reliability with which we can be sure that two and two make four. The first of these lines of attack is what we shall call the *structural* side—the discovery and study of the way in which substances are put together or constructed; the second line of attack we may call the *functional* side—the discovery and study of the laws controlling the way in which substances act upon one another.

We may compare these two lines of attack with the way in which visitors, say from Mars, would study what would be to them the mysteries of our terrestrial civilization. For instance, in a study of New York City a whole group of Martian architects would be kept busy examining minutely the mode of construction of the sky-scrapers from their deep-set foundations, through the steel skeletons, to their thousand elaborate details of utility, convenience

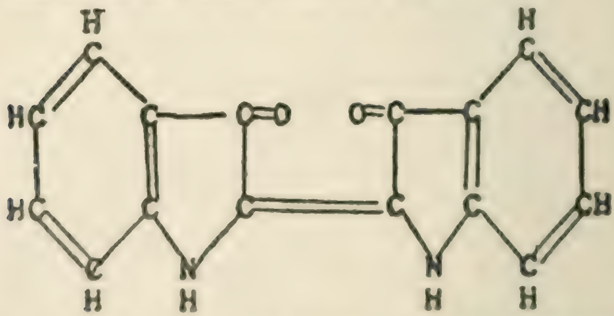
and decoration; they would study the construction of residences, apartment houses, tenements, bridges, streets, railways, subways. But quite another group of men would be especially devoted to the study of the laws governing the streams of life pouring through these structures, banks, post-offices, factories, subways, and hundreds of other units of the great life of the city in the act of functioning.

Constructive Chemistry Based on Minute Analysis;—Creative Chemistry.—Taking up first the structural line of attack by chemistry in the study of the transformation of matter, we find that chemistry aims to analyze every material that comes under its ken in the most minute fashion. It first separates and isolates the pure principles, scores of which may compose a mixture such as our blood. It studies the properties of these pure principles minutely and then it proceeds even to a far finer analysis; it takes these pure principles apart to their *very atoms* [1]—indeed it is now engaged in dissecting and analyzing the very atoms themselves—exactly as a bright-minded boy would take his watch apart to the last screw and wheel or his auto-engine to the last bar and nut. This ultimate or molecular analysis, as we call it, can satisfy only in part the chemist's unconquerable determination to know *all* about the thousands of principles he is able to isolate in this world of ours; for having taken the molecules of important principles apart and studied how atom is united to atom, often dozens of them in a single molecule, he does not rest until he has succeeded in reconstructing

[1] Thus, the smallest particle of water (its "molecule") is found to contain one atom of oxygen combined with two atoms of hydrogen and chemists express its "structure" by the formula H-O-H. Most important principles have far more complex structures (see below).

(synthesizing) perfectly his principles [1]—very much as the ambitious boy will not rest until he has reconstructed his watch or his auto-engine. Having thus acquired complete knowledge of the ground plan of important principles which we find in nature, the chemist in many an instance has found it possible *to improve on nature* and construct *more perfect* principles—exactly as in the experience of the writer, lads taking the engine of a motor boat apart were able by ingenious improvements to reconstruct it with an increase in its speed and power of 20 to 25 per cent—exactly, indeed, as human intelligence has always improved on nature, leading the race from gloomy, damp and uncomfortable caves to houses growing ever more perfect and convenient, improving the quality of animals by domestication, raising the yield of the soil by fertilization, and protecting and aiding humanity in thousands of other directions. It is this insistence on complete ultimate analysis which gives to chemistry one of its most

[1] Thus Baeyer showed that indigo has the structure



The letters C, H, O and N signify atoms of carbon, hydrogen, oxygen and nitrogen, and the lines joining them show how the atoms are linked up in the molecule. It took fourteen years for Baeyer to solve this problem—with the result ultimately that Germany succeeded in making real indigo out of coal tar of an annual value of millions of dollars.

powerful resources—for with complete knowledge comes *control,* in the form of wise use of what nature offers and also in the opportunity for improving on what nature, blindly, has furnished to man.

Chemistry Goes Far Beyond the Range of the Microscope in Biology and Medicine.—A simple consideration from the point of view now gained will reveal at once why chemical investigation has become a most powerful instrument in biological, in medical research: it is well known that in the past biology and medicine have used as their greatest instrument of precision the microscope, which led indeed to the great discoveries of the cellular structure of living matter, of the germ theory of life—as opposed to the exploded theory of spontaneous generation—of the germ theory of diseases, etc. But the microscope, with all its marvelous improvements, can go no farther in analysis than the cell and its divisions—whereas chemistry can and does go much farther. For within the boundaries of even a minute cell, there are dozens of different principles, there are myriads of molecules, which defy the power of the finest optical instruments; but they are subject to the keen, patient, analytical and synthetic quest of the chemist! "There is a constant molecular interchange between the cell and its environment." "Cell-secretion, cell-respiration and cell-nutrition are clearly only different aspects of the same whirl of molecular activity." (Haldane of Oxford.) In a word, chemistry is now called upon to provide the medical investigator with the most powerful ultramicroscope the world has ever known, to lead him far beyond the limits of his present bounds of knowledge. This in short is the reason why

medicine and biology in general have found it necessary to turn to chemistry for the final solution of many of their greatest problems: the old methods stop at the limits imposed by the microscope—with the invocation of the aid of chemistry there is no limit to ultimate analysis, down to the minutest particles, the molecules and atoms. In turn, the chemist needs in this service the advice, indeed the undivided coöperative effort of the medical investigator, the pathologist, bacteriologist, internist, for only such coöperation will bring the vital problems of medicine home to the consciousness of the experts in the fundamental science: What the naval and army experts meant to the research staff of the Chemical Warfare Service, the medical leaders must mean in this proposed coöperative attack on disease with the aid of the fundamental sciences of life.

What the Chemical Method Accomplished with Dyes;—Complete Conquest of Color Production.—We will the better appreciate the vital possibilities of this partnership, if we turn for a moment from the consideration of chemistry and medicine to observe what a complete triumph has already been brought to mankind by exactly this type of chemical investigation in the domain of dyes. Originally dyes were obtained exclusively from natural sources—indigo and alizarin or turkey-red and a few others from plants, carmine and some others from animal sources. Then, in 1856 Sir William Perkin accidentally prepared the first aniline dye mauve (while trying to make quinine artificially), and after that chemists from time to time stumbled similarly on other even more valuable dyes, magenta, methylene-blue, the beautiful rhodamines, etc. Already in the sixties, pio-

neer chemists started on the finest ultimate analysis of the dyes—determining in fact the exact way in which the atoms in the smallest particles of each dye are joined together. Graebe and Liebermann succeeded in doing this for alizarin (turkey-red), Baeyer for indigo, Bernthsen later for methylene-blue, and others for a number of other fundamental dyes. The results of this exploration of the ultimate minutiæ of dyes has been the complete conquest by man of the domain of color production: alizarin was at once made from coal-tar products previously wasted, instead of being obtained from madder, and large acreages were turned from the cultivation of madder to the growth of wheat and other needed crops. Indigo is now made artificially of a purity greater than that of the natural product (because free from admixed rubbish and foreign dyes) and the indigo fields are giving way to food crops—a distinct gain to man. Even more important is that by comparative studies of the structures of the molecules of a number of dyes, the key to the whole mystery of color production and color quality has been gained by man, with the result that we can now produce dyes of any given qualifications as to color, shade, stability to air, to light, soap, and water, sensitiveness to light (for photographic purposes) indeed even of two colors combined in a single dye (as in the beautiful fluorescent shades in silks).

Ultimate Conquest of the Chemistry of Life.—This complete conquest of the domain of color occupied some forty years; is it surprising that chemists are quietly but absolutely confident, with the aid of the biological sciences and of physics, of an ultimate conquest in the domain of life products, of medicine by giving to biology the service of these

same methods of complete ultimate analysis? But they do realize that where a little over a generation sufficed for the conquest of the domain of color with only a few dozen fundamentally important dyes, life with its thousands of important components will be a far greater, as it is a vastly more important field of conquest, requiring generations of intensive workers. But that emphasizes so much the more the urgent need for a concentrated, multiple attack—so that time may be saved by swifter progress year after year.

III. *Constructive Chemistry in the Service of Medicine*

After this preliminary survey of the aims and resources of this phase of chemistry, let us ask now without further delay, what specific services *constructive chemistry* can and must render to *medicine* in the prevention and cure of disease. We find that chemistry from its constructive side can be of greatest services in three specific lines of attack, which are arranged not in the order of fundamental importance but rather in the order of simplicity of attack and consequent promise of comparatively earlier success:

Lines of Attack.—1. The preparation of the specific medicament for the cure or alleviation of the specific disease.

2. The isolation, study, and, if need be, the artificial preparation of pure organic principles of fundamental importance to our life, such as principles of secretion of the body organs, of which a deficiency or an excess would cause disease (goiter, acromegaly, dwarfism, gigantism, and probably diabetes, gout, etc.).

3. The complete ultimate analysis of the con-

stituents of our body cells, of the components of the blood, of tissues, together with the complete ultimate analysis of the components of our foods—so that we may have complete knowledge of the body in health and of what it needs to preserve its health.

The Specific Medicament.—Taking up first the problem of the specific medicament for specific purposes, we find chemists engaged in two lines of efforts: in the first, they start from natural remedies already known, examine them exhaustively and with the knowledge gained improve on the natural product; in the second line of effort, they start out independently of natural drugs and attempt to prepare the specific remedy for the destruction of the specific invading germ, or the specific remedy for some faulty adjustment of the human organism in disease.

The Story of Cocaine and Its Promise.—A brief survey of the results obtained from the study of the drug cocaine will illustrate sufficiently the value of the effort to improve on natural remedies. Cocaine is a white, crystalline substance, like salt or sugar, which, brought in dilute solution (4 per cent) on the tongue, under the eyelid, or injected under the skin, was found by Von Anrep to suppress locally all sensation of pain. It was first used in surgery by the ophthalmologist Koller, of Vienna (now of New York), and proved to be an invaluable aid to surgery for the production of local anæsthesia, making possible painless operations without recourse to general anæsthesia under ether, chloroform or laughing gas. But cocaine had three grave defects: one, its rareness and resultant expensiveness, which limited its usefulness, the other more serious defects that it is difficult to sterilize, and especially that it is decidedly poisonous and occasionally in minor operations—in those of dentis-

try, for instance—fatal results ensued not warranted by the conditions. Cocaine then fell under the searching scrutiny of chemists, who subjected it to ultimate analysis for the determination of the structure or the arrangement of the atoms in the smallest particle, the molecule of cocaine; there are no less than 43 atoms in this molecule, arranged in a peculiarly complex, labyrinthal fashion [1] and it took three successive attacks by leading chemists to reach a final solution of the problem. With this vantage gained at however great a cost of mind and labor, the problem of local anæsthesia immediately made tremendous progress. It was found that only part of the molecule has the beneficent anæsthetic effects of cocaine, while another part is closely related to the deadly principle of hemlocks, coniine, famous as the poison Socrates was forced to take, and a third part is related to nicotine.

Improving on Nature.—And now the chemist was in a position to improve on nature and invent local anæsthetics with the virtues of cocaine and without its excessive toxicity—exactly as a conscientious modern architect in planning a house would insure the absence of noxious rooms deficient in air, light, heat or drainage. We have now, in fact, a number of those artificial local anæsthetics—pro-

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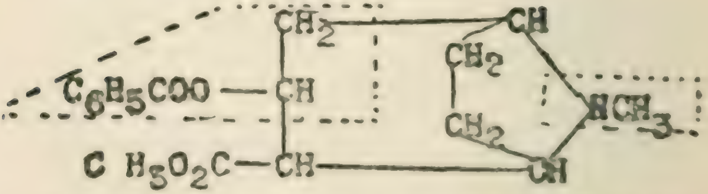
[1] The structure of cocaine is indicated by:



Only the parts surrounded by dotted lines are of value in producing local anæsthesia.

caine (introduced as novocaine), beta-eucaine, apothesine, etc., and, more recent, benzyl alcohol and related products—better than cocaine, because less poisonous. The extent to which they are being used in surgery is growing very rapidly and they hold out to man the possibility of some of the greatest advances of the future in this field; even major operations, for appendicitis, hernia, uterine troubles, are being performed now under local anæsthesia, and it is to be hoped that the field of general anæsthesia, with its grave fundamental principle of poisoning the whole system with ether, chloroform or laughing gas, will grow more and more limited to unusually prolonged or unusually painful operations. We have here, then, a first real triumph in medicine of the science that triumphed so completely in the field of dyes. In itself, this successful effort has been an untold blessing to thousands of sufferers, but the great lesson the story of the conquest of local anæsthesia teaches is that it is a golden promise of ultimate victory heartening the army of chemists in their grim onslaught on the more profound and vast problems of the chemistry of all life.

Chemistry Contrives the Cure of Leprosy.—Another rather recent, and in many respects a most important instance of this kind, is the specific remedy used with much success in the treatment of leprosy: chaulmoogra oil is an irritating, nauseating natural product, used for perhaps sixty years in India in the treatment of leprosy. Even in those days of uncertain quality and uncertain method of administration, the oil proved its usefulness, but a positive and most signal advance in the successful treatment of the disease was made only through the isolation by chemistry from the nauseating natural product of clean, pure acids which were combined with ethyl

alcohol and thus formed a new drug which could be used hypodermically. In a recent publication, 78 cases of apparent cure by this improved drug have been reported. While even greater improvement in the medicament is looked for by further painstaking research, we have already an effective remedy for one of the most hopeless of diseases—a result of the active coöperation of medicine and chemistry.

Some Other Improved Drugs.—Improvements of other natural drugs have similarly been accomplished. A few instances must suffice here. Atropine, as used by the oculist, puts the eyes out of commission for two or three days—the chemist has supplied homatropine for the busy man, reducing the effect to two or three hours. Morphine, the Dr. Jekyll and Mr. Hyde of nature's store of remedies, with its blessed alleviation of pain, carries the curse of the habit-forming drug. Chemistry found with morphine the drug codeine, also in opium, whose effects resemble those of morphine except that it is very much less likely to produce habit. There is little codeine in opium, but again chemistry easily converts morphine into codeine, giving mankind an ample supply of the blessed sedative shorn of its curse. Morphine is similarly readily transformed into ethylmorphine (dionine), which resembles codeine in its action and which has also found important applications in the treatment of certain diseases of the eye.

Chemists Aid in Diuretics.—In 1886 the pharmacologist, W. Von Schroeder, first studied by experimental work on animals the diuretic action of caffein and attempted to explain why this drug was uncertain and not always reliable as a diuretic. Chemists had, however, found another principle, theobromin, very closely related to caffein in mo-

lecular structure and composition. What was more natural for the experimental pharmacologist than to try the effects of this close relative of caffein to which chemical study had pointed? And, in fact, theobromin was found far more useful and dependable than caffein in its diuretic action and has largely replaced it. Still a third related compound, theophyllin, was discovered by chemists and found the best of all. The natural supply of these drugs being rather limited, chemists solved in short shift the task of preparing them artificially in any quantity desired.

Chemistry May Help Cure Pneumonia.—Profound study of other natural medicaments should be pursued with great intensity; there is every reason to believe that a modification of quinine can ultimately be prepared which will be a specific cure of pneumonia. One modification, optochin (ethyl hydrocupreine) is already known to be a specific in killing pneumococcus germs in glass vessels (*in vitro*) and is used successfully in external pneumococcus infections, as of the eye, but it is still too poisonous to be used in sufficient strength in the blood to combat the hosts of invading germs in pneumonia itself. No greater blessing could be granted mankind than the discovery of such a specific, as pneumonia is one of the two diseases responsible for the greatest loss of life in the world (tuberculosis is the other one). The tragedy of the situation is the tremendous waste of life, for instance during the recent influenza epidemics, while the preparation of such a specific is being looked for.

Save Time and Life.—No matter how ardently, how skilfully, the work is being pursued, the lesson of the past teaches us that only by a massive coördinated attack of many workers can we hope to

save time and all it means to us. A generation ago one of the greatest specialists in children's diseases in New York City lost his only son through diphtheria. It was a heart-breaking tragedy for him that science had not brought diphtheria antitoxin into the world just a few years earlier, so that he might have saved his own son. In how many thousands of homes is this tragedy being reënacted today in the face of diseases which man ultimately must and will conquer.

The Story of Arsphenamine the Specific for Syphilis.—Chemists, as stated above, are also attacking the problem of the specific remedy for the specific disease quite independently of any compounds that nature has supplied. The greatest instance of this kind is arsphenamine ("606" or salvarsan), prepared by Ehrlich as the result of a systematic effort to prepare a drug that would kill the invading germs, the spirochetes of syphilis, without injury to the patient. It is again to be noted that this first great successful attack on a most widespread disease was brought to a successful issue by the closest coöperation between chemistry and medicine. Dr. Ehrlich, from his earliest years in medical investigation (1884), was characterized indeed by the application of chemistry to his problems. His first research work was on dyes used as stains, a chemical problem. The very name "606" indicates how he gradually accomplished his purpose—using first one substance of a definite known molecular structure, then another, until seeing improvement ahead, he modified first this and then that part of the structure of his molecules until finally complete success was accomplished after 605 imperfect results, exactly as the sculptor models from his coarse clay the perfect head through a long series of incomplete, imperfect

stages. The tremendous value to mankind of this brilliant chemo-medical triumph is realized when we recall, first, that "606" and later developed drugs of the same kind properly used are specific cures for the disease syphilis, and, second, that this disease is so widespread that it has been estimated that in the United States alone we have over ten million cases of the disease in its various stages and dread sequels.

A Chemical Synthetic to Relieve Gout.—Another notable instance of the artificial chemical remedy is cinchopen (introduced as atophan), the uric acid eliminant, an alleviative, and in some cases a preventive, in gout.

Campaign of Conquest in Sedatives;—A Chemical Specific in Epilepsy.—In the field of hypnotics, used to produce sleep and allay nervous excitement (insomnia, epilepsy, etc.), constructive chemistry has advanced far its campaign toward complete conquest. The advance has been made from the earlier and sometimes dangerous hypnotics, chloral and its derivatives (great blessings in their day but dangerous because highly toxic, like chloroform), from the habit-forming sulphonals and trionals, to such hypnotics as barbital (introduced as veronal), luminal and adalin, which are very closely related to products formed naturally in the body, and produce sleep with a minimum of disturbance and risk to the system. Luminal is claimed to be a specific to relieve, indeed to prevent, the seizures of epilepsy. The importance of this invention of modern chemistry was revealed during the war years when exhaustion of our supplies of the drug brought in its wake pathetic and fruitless appeals from nerve specialists, hospitals, patients and parents.

Hookworm Cured by Chemicals.—Another dis-

ease for which a specific chemical cure has been found is that caused by the hookworm, affecting over a hundred millions throughout the world and widespread in our own Southern States. It is one of the most debilitating of diseases. The chemical thymol in conjunction with chenopodium has been found to be a very effective agent in the cure of hookworm, but again it is confidently expected that some modification of thymol could be elaborated by synthetic chemistry which would be even more efficient, and would lead ultimately to the complete elimination of this disease from our country.

Three Scourges Lack Specifics.—There is a tremendous, practically undeveloped field for greater work here—specifics are most needed now for tuberculosis and pneumonia, and perhaps even for cancer, to which a large proportion of mankind falls a victim.

Need for Coöperation;—Needless Suffering.—In any efforts in this direction, we must always remember that the greatest promise for success would be found only in closest coöperation of chemists, pharmacologists and medical men. The past is replete with impressive lessons emphasizing the importance of such coöperation. Two or three instances must suffice to show how important this lesson of the past is. Five centuries elapsed between the discovery of ether by chemists and its application for surgical anæsthesia, five centuries of needless suffering. The first chemical used to produce sleep, chloral hydrate, was known to chemists for almost forty years before the pharmacologist Liebreich discovered that it produced in pain-racked bodies a peaceful sleep from which after a few hours the patient awoke greatly refreshed. Many other

hypnotics and sedatives were then soon found among compounds long known to chemists.

All of Ehrlich's great work on the cure of syphilis was accomplished when he was between 54 and 61 years of age, but following lines of thought which had been in his mind for 30 to 35 years; he had been waiting all that time to get the full coöperation of chemists, and this became possible only through the munificence of Frau Speyer in Frankfort. More was then accomplished in four years by chemo-medical research than in four centuries of medical effort, including hygiene and education.

An End to Agony.—Amyl nitrite was discovered by a French chemist in 1844, but it was not until 1867 that it was found to give relief from the agonizing pains of angina pectoris. Dr. Brunton, led by the results of experiments of the pharmacologist and biochemist Gamgee, made this discovery and thus describes the first case in which the remedy was used by him: "There was one poor man in the wards suffering dreadfully from angina pectoris; he used to have an attack every night and for two hours the unfortunate man would sit on the edge of his bed and could not move forward, backward, or to one side, with his face pale and sweat pouring off it, in perfect agony. The administration of amyl nitrite gave him instant and complete relief." There are tens of thousands of persons in the United States alone afflicted with this dread disease of the heart, to whom amyl nitrite is a blessing indeed. These tragic delays resulted from the wide gap that existed between the scientific activities of investigators in medicine and in chemistry; they must in future be prevented by intensive, closest coöperative effort and interest.

The Problem of Hastening Relief.—There are

hundreds of thousands of sufferers from painful, consuming diseases for which the remedy awaits the joint intensive efforts of chemist, pharmacologist and physician. How many years must they wait? That is our problem.

Pure Principles of Secretion:—The Story of Epinephrine.—The second great field of effort for the constructive chemist is the isolation, study, and if need be, the preparation of pure principles of our organs of secretion and of other principles of vital importance to healthy life. One or two specific accomplishments will illustrate the vital importance of this work. After Schafer and Oliver, Szymonowicz and Cybulski had noted the presence of a vasoconstrictor principle in the suprarenal glands, small glands situated just above the kidneys, Professor Abel, of Johns Hopkins University, succeeded in isolating this principle, epinephrine (adrenalin), in the form of a derivative and prepared a number of salts of this derivative. Later J. Takamine precipitated the pure principle itself by means of ammonia, a precipitating agent which Professor Abel had already used in this work, as the native compound in the form of minute crystals. Its chemical structure was later determined, with the result that epinephrine can now be prepared artificially. The manufacturer's patents having expired (in February, 1921), the world is the richer for wide sources of manufacture of this invaluable drug. Some of the very great advantages of the isolation of this pure principle are these: It is injected with local anæsthetics (procaine, etc.), causing constriction of the blood vessels and preventing a rapid local loss of the anæsthetic, thus reducing the amount needed very materially and reducing correspondingly the danger of toxic effects. Injected hypodermically,

epinephrine allays within a few minutes the spasms of acute bronchial asthma, an untold blessing which those can only realize who have in the past witnessed helplessly the acute sufferings of a patient. Epinephrine may also be used for the quick arrest of hemorrhage of a capillary or small arterial character—all blessings for man.

Epinephrine Sustains the Heart in Operative Cases.—Very recently (unpublished work of Dr. Miller, of New York City) perhaps the most important of all uses of epinephrine has been discovered: this is based on its action on the heart. Injected in such a way as to provide for very slow and gradual absorption, it is of extraordinary value when used in preparing old or weakened patients for operations, fortifying the heart against the danger of shock and failure.

Epinephrine in Pneumonia.—Of equally great value is the injection of epinephrine in this manner in the treatment of pneumonia. Used from the earliest stages, it reduces the danger of death from heart failure to such an extent that eminent physicians with its aid feel safe in depending on the normal resistance of the body to effect a cure of this dangerous disease, thus avoiding the dangers of antitoxin injections. These discoveries of today emphasize the vital importance of exhaustive investigation by the joint efforts of chemist, pharmacologist and physician.

Thyroxin by Chemical Conquest.—More recently Dr. E. C. Kendall, of the Mayo Foundation, has isolated thyroxin, the crystalline active principle of the thyroid gland, which regulates the metabolism (the combustion of our food) of the body. This principle is so tremendously active that an occasional dose of a fraction of a milligram (a

minute fraction of a grain) is able to cure cretinism, a condition of stunted growth of body and mind, and myxedema, a similar condition developing in adults. The artificial preparation of thyroxin is only a question of time and effort and one more outpost of the bulwarks of life will thus have been conquered by the chemist.

Problems Yet Untouched.—There are many other vital secretions the isolation of whose pure principles must be undertaken: the isolation of the active principle of the pituitary glands, controlling of normal growth, the isolation of further active principles of digestion and metabolism (for the cure of gout, diabetes and other metabolic diseases), the isolation of the active hormone controlling normal sex functions, are a few of the great problems lying almost untouched for lack of workers in the field of chemical effort in the service of medicine.

Pure Principles of Antitoxins;—Advantages of Pure Principles.—Another great line of effort in this direction should be the attempt to isolate the pure principles of antitoxins, bacterial vaccines, and serums now used so widely in the cure or prevention of infectious diseases (diphtheria, tetanus, streptococcus infection, meningitis, etc.). The fluids which are now injected contain, no doubt, only very small quantities of the pure, active principles, mixed with a vast proportion of inert and in part harmful matter (horse serum, etc.). Every physician of standing has rejoiced to have been delivered from the old days when, to secure the effect of strychnine, he was compelled to prescribe tincture of nux vomica of an indefinite composition, when to produce the effect of quinine he had to prescribe ground cinchona bark, etc., etc. Chemists isolated strychnine, quinine, morphine, atropine.

cocaine, hyoscyamin, pure principles from the crude drugs offered by nature, with the tremendous advantages, first, of quantitative accuracy in administration replacing an approximate and sometimes disastrous guess, and, second, of putting into the hands of physicians the possibilities of almost instantaneous effects by hypodermic injections of pure solutions of the pure principles. In the course of time it must be chemists again who will place in the hands of the physician the pure active principles of the antitoxins, vaccines and serum mixtures, which are the real curative principles and whose action must at best be handicapped by the presence of a preponderance of useless impurities injected into our veins and tissues. The isolation of such specifics should be followed by the exhaustive minute study of structure, revealing the why and wherefore of action, opening up the way possibly to refinement and improvement.

Our Greatest Need.—How immediately urgent intensive work of this kind must be considered is brought home to us by the heartrending helplessness of physicians in the presence of certain sudden diseases when patients full of strength and vitality and otherwise healthy, nevertheless face extinction because of the inability of the ablest of physicians to reach the source of destruction. The treatment of pneumonia by antipneumococcus serums holds out great promise of successful combating of one of our greatest scourges in at least a fair proportion of the cases. But it is well understood among physicians that the injection of large quantities of serums in such treatment may be attended by new and serious dangers of anaphylactic shock and other complications. These difficulties without doubt would be decidedly lessened if chemists succeeded

in separating from serums the minute amount of pure, active principle which must be present. This problem, with others of the same character, is perhaps the very greatest immediate problem awaiting the attack of chemo-medical research—and scarcely a start has yet been made toward the goal!

Endocarditis a Helpless Tragedy.—Endocarditis, an infection of the valves of the heart, is another disease before which medicine stands practically helpless, although the victim may be a young man or young woman in the bloom of life and otherwise in brilliant health! It is scoring its tragedies among rich and poor, the well-protected and the most exposed, by the thousand each year. Antitoxins, auto-vaccines, serums are used but are of little avail, although it is known from laboratory experiments that in sufficient doses they should kill the invading germ. Again, it is most likely the huge quantity of useless impurities, such as horse serum, which limits the physician in the application of these remedies. Might not relief be found in the swift, sure action of the pure, active principle, to which the germ is sensitive, injected intravenously in measured strength, bereft of its present load of ineffective impurities, before the germ has itself become immune to the principle? In the present state of tragic helplessness, the effort certainly would be worth making.

Health and Food.—The third great field of effort in behalf of medical science by constructive chemistry is found in the exhaustive study of all the important components of the cell contents and tissues and fluids of the body carried out parallel with a similar exhaustive study of our food resources. The Martian architects studying the structures of New York City in the way suggested

above, must need examine and understand every part, large or small, entering into the edifices of the highly complex community if they would undertake to keep the city in first class repair and working order under the stress of the tremendous wear and tear of the life flowing through its veins. Thus, they would insure that into the city are brought all of the myriad parts, or the materials for their manufacture, needed for replacement and repair, ranging from obvious rail, brick, stone, terra-cotta, tile, beam, to the hidden finest bolts and screws, levers and wheels of the controlling devices of elevators, of lighting, water, plumbing, drainage systems.

Chemists Analyze Food Products.—In the same way, the body demands an impressive variety of materials for its healthy sustenance. In its blind effort to contribute these, a part of humanity has been inclined to overeat, with its resultant ills of functional disturbances. Another large proportion of humanity has been well nourished in quantity but undernourished in regard to particular units of sustenance—with the resultant diseases of nourishment, beri-beri, pellagra, rickets, etc. Much work has already been done by the chemist in the exhaustive analysis of food products, such as carbohydrates, fats, amino-acids, but only a beginning, however important, has been made, and every result demonstrates more convincingly the need of a much more complete knowledge.

Fundamental Chemical Study.—The fundamental work of the chemist, Emil Fischer, on the structure and chemistry of the sugars opened the gates for all the more recent work on carbohydrate metabolism and its pathologic variations as found in diabetes. Again Fischer's work on the amino-acids,

a purely chemical study, forms the very foundation of all modern work on protein metabolism, on protein functioning. With the aid of the pioneer work of this chemist, recent work has shown that while the human body can construct a considerable number of its needs from the common ingredients of all foods, there are other vital, specific needs which must be supplied to it in finished form or else starvation of vital parts and disease and death follow in the midst of what otherwise would be plenty. It will be the duty of chemists to furnish a complete statement of such specific needs, to show just how they can be satisfied, to help out perhaps, indeed, by showing how certain rare and difficult units can be manufactured artificially.

Some Recent Victories;—Scurvy Cured and Prevented; — Goiter Attacked. — Indeed, coöperation between medicine and chemistry has already scored important victories in this field: Diseases such as scurvy and beri-beri have been found by physicians and chemists to have their source in the lack of certain minute but vitally important principles—hence called vitamines—found in some but not in all foods, and with these discoveries and the results of the analysis of a great variety of foods properly brought home to the practitioner the world over, these diseases should vanish from the face of the earth. Again, in the thyroid gland minute quantities of the chemical element iodine are found. Its absence in the diet is likely to cause thyroid trouble such as goiter. The observation that goiter is very prevalent around the Great Lakes, especially in young girls and young women, led to an attempt to prevent the development of goiter in a town in Ohio by the giving of small quantities of sodium

iodide to the schoolgirls for short periods. The results under competent medical direction have been astonishingly good, and there is no question but that this simple instance of coöperation between chemistry and medicine will lead to the prevention of many thousands of cases of disease with its attendant dangers and unhappiness!

Mental Problems.—That the possibility exists that certain mental disorders may be produced by chemical principles taken in with our food or by toxic principles produced from our food under abnormal conditions is shown by the fact that certain chemicals are well known to affect the mind: In Beverly's "History of Virginia" in which Bacon's Rebellion is described, a striking instance of the kind is found, where a company of soldiers partaking of a certain herb (Datura Stramonium, containing the principle hyoscyamin) were for a time rendered ludicrously "foolish" with all the symptoms of temporary insanity. Other chemicals when inhaled are well known to laboratory workers as extraordinarily and permanently dangerous to the mind. Exhaustive, patient work of the chemist side by side with the medical observer is needed to bring light into this at present utterly dark, unexplored field. The hardening of arteries—the common enemy of man after he has passed middle age—again is very strongly suspected of being largely dependent on little understood nutritional factors. With its resultant serious diseases—high blood pressure, kidney and heart troubles—we have here again an invaluable field for research by the painstaking complete analytical methods of the chemist, which may ultimately give the physician the knowledge to prevent the effect and its consequences.

IV. *Physical Chemistry and Physics in the Service of Medicine*

Life Is Dynamic.—We have been considering thus far some of the accomplishments and the more numerous problems in the service of medicine of only one of the two great methods of attack of chemistry in the great study of the transformation of matter—namely, of what we have called *constructive* chemistry, dealing with the minute analysis of the composition of matter and with the building up or synthesis of matter on the basis of the knowledge thus gained. There is, as was stated at the outset, a second equally important method of attack—the study of the functional or dynamic side of the transformation of matter—comparable, as will be recalled, with the study by our visiting Martians of the life pulsating through our million edifices in New York City as contrasted with the study of the structures of the city by the architectural group.

Physical Chemistry.—This phase of the profound study of the transformation of matter is called physical chemistry, involving the applications to chemical change of principles of physics, the fundamental science of the transformation of energy (of forces, of motion, etc.). It concerns itself primarily with the laws of chemical change, the limits and controls of action. The two kinds of chemical investigation go hand in hand, but the fields are so enormous and difficult that as a rule men are specialists in one field or the other and only in rare instances have expert knowledge in both fields. Quite obviously, since life is dynamic, medicine must call into its services the physical chemist, as well as the constructive chemist, as we have labelled them.

The Time Factor in Life.—A few illustrations of

past accomplishments and of future problems must suffice in the attempt to elucidate the innumerable applications of physical chemistry to medicine. The greatest factor distinguishing dynamic action, such as we have it in life, from a static condition, is the *time factor*, the *speed factor*. Life is dependent in an unusual degree on the proper, fine adjustment of the time relations of a great many interdependent actions in the body: the rate of the heart-beat (the pulse), the rate of respiration, the rate of metabolism (the speed with which our food is consumed in the blood, tissues, etc.), the rate of digestion, the rate of elimination by the kidneys, skin, lungs, etc., are all of the same vital importance to the smooth working of the healthy body, as in any engine the rate of the flow of gas, the rate of combustion, the movements of pistons, valves, etc., are for the smooth and perfect working of the machine. In fact, the wonderfully fine adjustment of these speed factors in our bodies to the needs of life and their marvelous capacity of self-regulation and readjustment under disturbed conditions form perhaps the most impressive element of life when viewed from the standpoint of its material transformations.

Physical Chemist Discovered Laws of Health Control.—It is the physical chemist who has discovered the laws of the speed of chemical action—on which all of the time factors of the body ultimately depend—and to the physical chemist medicine is turning for aid in the solution of these problems in the control of health.

Healthy Digestion versus Dyspepsia—and the Time Factor.—As an elementary illustration, let us consider digestion, in which we are all concerned. Anyone interested in the question of the speed of digestion can prepare a very hard boiled egg (10

minutes), separate the white of egg from the yolk and press the former through any kind of sieve at hand; equal portions (teaspoonfuls) are then placed in three glasses of water, kept at body temperature or a little higher (100° to 120° Fahrenheit) by being placed in a larger vessel of warm water, the contents of the three glasses being stirred by paddles moved with the aid of a little water turbine or a small electric wheel. The three tumblers thus prepared represent artificial stomachs. To the one glass is added both pepsin and two or three drops of dilute hydrochloric acid, to the second only the acid and to the third only the pepsin. If the higher limit of temperature has been used (120°), the observer will note in about an hour or less that in the glass (stomach) containing both pepsin and acid, the egg albumin will have been dissolved—digested—this representing a normal stomach; in the other two glasses, representing dyspeptics lacking either acid or pepsin, there will be no digestion, that is, indigestion.

Acid and Pepsin Functions Not Wholly Known.—Now, it evidently is of fundamental importance to us to know accurately just what the functions of the acid and of the pepsin are in speeding up (accelerating) the digestion of our food; no one would engage as chief engineer say of a war vessel or ocean liner any man who did not understand thoroughly the why and wherefore for every adjustment, every control in the complicated machine. And here we have in the (to us) most precious machines, our bodies, at the very outset an action which no man, physician or chemist, has to this day completely elucidated—the mechanism of the action of pepsin and acid in digesting our food at the very first stages of its absorption in our systems. The

physical chemist has clearly defined the laws and mechanism of related actions with acid alone, has made great progress in the study of the action of accelerators (catalyzers) in general; naturally, it will be to the physical chemist that medicine must turn for a more profound, more concentrated attack on this problem of digestion under the influence of acid and the peculiar digestive ferment called pepsin.

Accelerators Controlling Factors.—Pepsin is but one of a very large number of accelerators or catalyzers—called *enzymes* technically—which are the speed regulators of all of our body functions. The digestion of our food in the stomach and intestinal tract, its transformation into new materials in our blood, and its storage in our organs, its combustion in the blood and tissues, all are subject to these controlling factors. And not a single one has been completely mastered as yet by the mind of man.

Acidity Affects Health.—In the little experiment tried above, the absence of acidity was observed to be quite as pathological as the absence of pepsin—and as a matter of fact the presence or absence of acidity, or in certain cases, of its complement, alkalinity—is another of the great controlling factors in the healthy functioning of the body. Proper acidity of the stomach facilitates digestion—acidity of the blood or tissues on the other hand is most detrimental to combustion of our food; hyperacidity of our renal secretions can be of the greatest danger to the secretory organs, the kidneys.

Self-Regulation of the Blood and Its Physical-Chemical Explanation.—Our blood has, however, a remarkable capacity to preserve its normal slight degree of alkalinity, to escape at the same time the Scylla of hyperacidity and the Charybdis of exces-

sive alkalinity. This wonderful capacity for self-adjustment and preservation of its optimum conditions for the purposes of life is a typical instance of innumerable fine mechanisms of self-adjustment in the body, all aimed at maintaining the most favorable environment for the functioning and preservation of life—self-adjusting mechanisms which in fact comprise for the scientific investigator the most impressive points of difference between living organisms and the lifeless world. And yet this remarkable power of the blood to maintain its normal alkalinity has been elucidated in a very complete way (especially by L. Henderson of Harvard University) by the application of simple principles of physical chemistry to the study of the composition of the blood: There are chemical "buffers" present, which act chemically to preserve neutrality exactly as powerful springs act as mechanical buffers to minimize the shock of impact to fast moving bodies.

It is well for us to recall, moreover, that the last generation of scientific workers could not possibly have elucidated this wonderful mechanism of self-adjustment, for the simple reason that the discoveries of the necessary fundamental facts and principles of physical chemistry which Henderson applied, simple as they are, *had not yet been made*. We must bear this lesson in mind when we face other mechanisms of fine self-adjustment for which at present we may be at a loss to find the key.

Body Work Subject to Physical Laws.—Another question of peculiar interest to man as a worker is the problem of the conversion of fuel elements in our food into work, comparable with the problem of the efficiency of the coal or oil consuming steam engine or of the internal combustion engine. This is essentially a problem of physics,

the fundamental science of the transformation of energy. Mayer more than sixty years ago called attention in general terms to the sources of energy for body work and emphasized the fact that living organisms are subject to the great physical law of the conservation of energy. In very recent years A. V. Hill of the University of Manchester has succeeded in applying in a masterly way the laws of physics in great detail to the working of a muscle.

Coöperation to Express Major Facts of Life.—It is work of this character, leading step by step to the complete understanding of most complex actions of our body by the application of the principles of physics and chemistry, which sustains the faith of those who believe that chemists and physicists, working in closest coöperation with the experts in the various fields of biology, will ultimately express all the major facts of the material side of life in their own exact terms and thereby give to medicine the control characteristic of an exact science. How necessary such encouragement of the faithful army of scientific workers is, must be apparent from the way in which so eminent a physiologist as Haldane of Oxford, in spite of his own brilliant work, *carried out with the aid of physics and chemistry*, on the fine adjustment of respiration to environment, despairs of the complete success of the fundamental sciences in explaining the automatic adaptation of the body to its life needs and to its own reproduction, and falls back on metaphysical conceptions.[1]

We need but recall that every modern machine, from the power engine to the loom, from the print-

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[1] Haldane, Mechanism, Life and Personality, 1914, and Organism and Environment, 1916.

ing press to the watch, is equipped with numberless automatically working devices of fine control and self-adjustment (such as the self-adjustment of a fine watch to temperature changes, by which winter and summer alike it will not vary a second in the ticking off of time). To the barbarian these man-made machines are as wonderful and complex, because not understocd, as are indeed the marvelously fine and sensitive powers of adjustment of the living organism to us, who still understand so little about them. Our problem without question is a tremendously complex one, but the advances already made are a sufficiently brilliant promise of ultimate success, and we can best hasten the advance by bringing together for closest coöperative work expert workers to form a small, well-organized corps, where in the past advance has depended most largely on the brilliant but dispersed sorties of the individual worker.

Colloidal Chemistry;—The Human Body Is Colloidal;—Bodily Stability Sensitive.—A further field of investigation for the physical chemist, which is of major importance to the development of medicine as an exact science rather than an art, is the study of "colloids." Graham distinguished crystalline substances, such as salt or sugar, from what he was the first to term colloids (from *colle*, the Latin for glue). Now the vital fact about colloids is that they do not dissolve, as would salt or sugar say, in water, but colloids form *suspensions:* milk is a common illustration of such a suspension of fat globules and of the cheesy components (casein) in a watery solution of milk sugar and some salts. Clay stirred up in water represents another well-known suspension. But the most important instance of colloids is the human body itself.

all of the tissues, muscles, fluids of which represent colloidal suspensions. It is for that reason that the exhaustive study of colloidal chemistry is of vital importance for the development of medicine as a science. Two or three specific illustrations of the nature of the problems we are facing must suffice here. It is well known to all of us that the very *stability* of such a colloidal system as milk is subject to disturbance by *small changes* in the system; acidity (souring) leads to coagulation, time or churning leads to the separation of cream and eventually of the butter. In either event, the milk as such is destroyed. All colloidal systems, and especially those of the body, are similarly sensitive to forces affecting their stability: the kidneys are peculiarly sensitive to acidity; the coagulation of our blood, the stiffness of our muscles are instances of disturbances of colloidal systems vital to our health. Milder disturbances lead to ill-health; severe changes, as the injection of acid into our veins, lead to death.

Besides the question of stability of our colloidal organs, tissues and fluids, another vital consideration is this: Since a colloidal system represents a suspension, we are dealing in every instance with at least two, and often many more, different media of entirely different properties. As the dweller on one of the Thousand Islands must live with the problem of water as well as of land, and must arrange for a system of communication by water and by land, so on the other hand the scientific study of our body is leading us to discriminate carefully between the needs of the watery fluids of the body and of the dozen different suspensions in us, fatty, gelatinous, protein-like, etc.

Surface Effects.—Surface properties of colloids

are of peculiarly great significance in life reactions —comparable roughly with the importance of shore facilities, of shore stability, to our typical island inhabitant. Surface tension, the force which makes the film of a soap bubble round and which may preserve it intact even when pricked by a fine needle, is found by physicists to vary greatly under stimuli such as electrical charges or chemical changes. It is known to play a fundamental rôle in life reactions such as in the motions of lower organisms, and the principles of surface tension must find a wide field of application in the study of the complex suspensions of our own bodies.

The Problem of Secretion.—Perhaps of even greater need of profound study are the adsorption and absorption phenomena of surfaces bathed by liquids; thus our organs of secretion, all colloids, have truly marvelous powers of maintaining conditions in the body favorable to life. For instance, the kidneys will prevent in very largest measure the diluting of our blood even when large volumes of water are imbibed: they respond at once, eliminating the superfluous water into the bladder as quickly as it is absorbed. In like fashion they rapidly eliminate excessive, injurious amounts of sugar, salt and other products liable to modify the character of the blood. The mechanism of selective secretion by the kidney, the mechanism, in fact, of secretion by any organ, is, in spite of many important investigations and their partial answers, still mainly an unsolved riddle to science. And yet there is no problem of greater importance to health in view of the vital rôle played by our organs of secretion.

Great Promise of Advance.—A more profound and exhaustive fundamental study of colloids holds out the greatest promise of advance in this direction:

let us recall that the neutrality of our blood could only be explained after physical chemistry had advanced sufficiently to give us the theory of "buffer" neutralizing agents, one of the consequences of the Arrhenius theory of ionization—a great and unknown field before the year 1887. Likewise the great problem of selective absorption by colloid organs is probably awaiting further advances in the fundamental sciences themselves.

It must be quite obvious that a concentrated attack on the problems of health and disease from the point of view of the fundamental sciences of chemistry and physics must include intensive study of the colloidal systems which form the major structure of our bodies.

V. *The Fundamental Problem—The Chemistry of the Body Cells*

In outlining the methods by which the fundamental sciences of chemistry and physics could contribute to the raising of medicine to the plane of an exact science in maintaining health and curing disease, we have thus far emphasized the possibilities for the solution of a number of specific and urgent problems, which, however difficult, hold out the promise of definite and not too remote success in a coördinated attack upon them by chemistry, physics and medicine: the preparation of specific remedies for specific diseases, the isolation of pure principles as swift, sure weapons to be placed in the hands of the practitioner, the protection of health by the exhaustive analysis of food, the profound study of our time reactions and their regulators, the study of colloids as the basis of investigation of our organs of secretion, are some of the points of vantage

toward which most likely the surest approach could be made. Success in these directions would bring unmeasured blessings to mankind in the prevention and cure of disease and the consequent promotion of happiness.

The Heart of the Problem—The Cell.—But the very heart of the problem of life, the highest form of chemical change, lies in the profound and complete study of the chemistry of the *body cells*, the units of which our bodies are composed. This is the most important, and also by far the most difficult problem of all: its solution is vitally necessary for that ultimate complete mastery of science over life, which will give man the wisdom to maintain health and increase the life span of the greatest number.

The Human Body Based on Cell Life.—If we let our minds dwell on the complexity of our body's structure and functions, we must recognize without question that man's body is not a primary form of life but the result of the slow processes of evolution from simpler forms through the ages. The whole history of the human race is indeed revealed to us in the most impressive fashion by the development of the embryo, starting with the fecundation of the minute human ovum, *a single cell*, and growing slowly by a rapid *multiplication* of cells to the fully developed infant as it appears at birth. Our bodies are, in fact, wonderfully organized communities of myriads of cells, the primal form of life. And all of our life functions are still carried out as in primal days by cell secretion, cell excretion and cell multiplication—the change of our food into body tissues, the elimination of waste products, the development of the means of procreation are but instances of this general truth regarding our body activities. Except for the extreme differentiation of functions of special

cells, we still live solely through the coördinated activities of cells.

Disease Often a Cellular Disturbance.—As a result the problem of curing or preventing disease is tending in an important sense toward a study of the means by which conditions for normal cell processes may be maintained or restored after any disturbance. In other words, we are being forced to conclude that the seat of disturbances leading to disease is the living cell which the biologist justly conceives as the unit of biological change. An active and normal cell development therefore means good health. These activities are fundamentally chemical and physical in character. Let us recall again: "Cell-secretion, cell-respiration and cell-nutrition are clearly only different aspects of the whirl of molecular activity" and "there is a constant molecular interchange between the cell and its environment." It is physics and chemistry that study natural phenomena from the point of view of molecular activities—it is to physics and chemistry that biology must turn for the ultimate study of its units of life, the cells, and we cannot overemphasize the importance of increasing our knowledge of the mechanism of the chemical processes operating in these hidden laboratories wherein all the fundamental reactions of life originate and take place.

Our Ignorance of the Chemistry of the Cell;—Living and Lifeless Material Undiscovered;—What of Heredity?—Now, while multitudes of definite chemical substances have been isolated from animal and vegetable tissues, the identification of which is a contribution to our knowledge of the chemistry of the cell, no comprehensive and exhaustive study of the contents of even a single type of cell has ever been attempted. In fact, it is only

when we begin to consider the cell from a strictly chemical point of view that we are led to recognize how scanty indeed is our knowledge of the chemistry of this vital biological unit. Thus, we do not even know in exact terms of physics and chemistry what the factors are that distinguish living from lifeless material: What are indeed the chemical and physical forces that lead to cell subdivision, the wonderful first step in life development? What are the forces that lead to perpetuation of life? To instinctive self-protection? What are the conditions for the equilibrium in the colloidal system we call protoplasm, which make an obvious difference between life and death? What is the chemical structure of proteins? Of the components of brain tissue, underlying the most wonderful of all life processes, consciousness, memory, thought, and feeling? What is the chemistry or the physics of the inheritance of body form from generation to generation, even of the finer traits of mind and temperament carried from parent to child through the minute cells of procreation? Are some of the millions of chemical molecules present even in these minute cells in some way the carriers of this wonderfully accurate transmission of qualities?

The Power of Knowledge versus Theory.—These are but a few of the extraordinarily important problems of chemistry and physics in the ultimate field of cell life. They are tremendous problems but many believe they are not beyond the power of the human mind in control of the scientific tools of chemistry and physics. Indeed, until these exact sciences do shed more light on these problems, there will be speculation, theory, philosophizing—but not knowledge. It will take many generations of many workers to attain this knowledge, but who can

question for a moment that complete success in these problems would spell for mankind health of the body, health of the mind, and the happiness of untold millions of sensitive beings! And based on this knowledge, the medicine of the future will finally succeed in attaining its present noble goal, to prevent disease, to maintain health, so that to a less degree there will be need of the combating of disease.

EXISTING FACILITIES FOR CHEMO-MEDICAL RESEARCH

In order to form a correct judgment in regard to the necessity for chemo-medical research, it is essential to make a survey of the facilities now available in this country and contrast them with the facilities existing in other countries.

Our own country, with its vast resources, should have a leading part in this important field of work; we cannot at this time escape the responsibility for contributing our full share to the alleviation of human suffering caused by disease, yet if we compare the number and scope of our own institutions for medical research with those of other countries it is evident that much remains to be done before we can aspire to leadership in this branch of research.

Facilities in the United States.—In commenting on Ehrlich's work in 1913, a popular magazine[1] said: "More immediately practical than any other scientific development of our time is the subjection

[1] Current Opinion, 55-256.

of the science of medicine to the principles of chemistry. . . . The importance of regarding medicine as a branch of chemistry and not as an independent science is manifest when we remember the therapeutic mysteries for a solution of which mankind is now desperately groping." The value of fundamental studies in relation to disease has thus been more or less generally recognized for a number of years, yet our survey shows that at the present time we are far behind Europe in our facilities for chemical research.

Chemical Standpoint Lacking.—While there are in the United States a number of institutes and foundations for medical research doing most valuable work, there is none in which the problems are being approached primarily from the chemical standpoint. Consequently few new lines of chemical investigation in relation to disease have been developed in this country and we have been largely dependent upon foreign countries, especially Germany, for discoveries relating to the applications of chemistry to disease. In considering the publications relating to chemo-therapy which have appeared in this country, it is remarkable to what a large extent they have followed a few lines opened up in Europe. Thus the many investigations on the therapeutic value of the newer arsenic compounds; the very numerous studies on the action of aniline dyes, including the combination of these with mercury and other metals and the work on the effects of quinine derivatives in pneumonia, are all based upon the work of Ehrlich. When Ehrlich laid the foundations for this work he was occupied with certain broad general problems (such as the laws governing the distribution of chemical compounds in the

body) and not with specific diseases. Work along these lines is already beginning to stagnate, and it is becoming more and more evident that new points of view are needed which can be obtained only by a return to the study of fundamentals.

It will be noted that many of the research foundations in this country have been established for the study of certain diseases, or classes of diseases, and are not therefore free to work upon broad, fundamental problems.[1]

Institutes and Laboratories in the United States

In the United States, medical research is conducted in universities, special institutes, Government laboratories and industrial establishments.

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[1] The importance, even for the solution of immediately practical problems, of opportunities to pursue fundamental studies irrespective of any specific disease is strikingly shown by the circumstances leading to the discovery of arsphenamine. Ehrlich was engaged in a study of the chemical and physical principles which determine the distribution of compounds in the animal body and had selected the study of dyes since their distribution was easily determined. While the purpose of these studies was purely theoretical, Ehrlich found that some of the dyes seemed to have a special affinity for blood corpuscles and thought that they might be of value in malaria. He accordingly made a series of experiments upon bird malaria and afterward determined the effects of the dyes upon parasites somewhat similar to those of malaria, viz., trypanosomes. Only after he had found what chemical groups made the dyes injurious to the parasites did he take up the study of arsenic compounds. He prepared compounds containing arsenic very similar, chemically, to some of the dyes and found that the same laws governed their trypanocidal action. He next tried these compounds upon the organism of syphilis which at that time was supposed to belong to the group of trypanosomes. In this way, from a purely theoretical study, Ehrlich was led to the discovery of "606."

If the activities of Ehrlich had been restricted either by the Government or by the terms of a bequest to a study of dyes or of arsenic compounds, or, on the other hand, to an effort to discover a remedy for sleeping sickness or for syphilis, it is not very probable that he would have been led to the discovery of the value of certain arsenic compounds in the treatment of syphilis.

Medical Research in American Universities.—Many of the leading University Medical Schools, although by no means all, have departments of Pharmacology. In these a considerable amount of valuable investigation on the action of chemical substances in health and disease is being done. Little of this investigation, however, relates to fundamental subjects; it consists rather in the detailed study of some substance, usually a well-known chemical compound, upon some highly specialized tissue or organ. Among the more fundamental subjects investigated in these laboratories may be mentioned pioneer work on epinephrine (adrenalin) and on the local anæsthetic properties of aromatic alcohols.

Instruction Limitations Common.—The primary purpose of these laboratories is the instruction of medical students, which of necessity forces the staffs to cover a wide field; this and the various other duties connected with an academic position allow comparatively little time for concentrated work on problems of major importance. Moreover, most of these departments are not in close touch with departments of chemistry, as the university pharmacologist and chemist are usually interested in chemical compounds from entirely different points of view: the pharmacologist from the standpoint of the therapeutist and physiologist, and the chemist from the standpoint of some general chemical principle. Exactly the same difficulties stand in the way of departments of bio-chemistry (physiological chemistry) as organized in most universities: primarily interested in the instruction of medical students, they are doing praiseworthy work, but necessarily limited in scope.

These circumstances, taken in connection with the

comparatively limited resources of the universities, make it improbable that the character of work in the minds of the committee can be satisfactorily accomplished in university laboratories.

Germans Grasp American Discovery.—As an instance of the severe handicaps placed on the university worker, the following is of interest: In 1910 a pharmacologist in one of our leading universities discovered and isolated from the contents of the poison glands of the tropical toad bufo agua a pure chemical principle, bufagin, which was found to have a marked and important action on the heart, of the order of the most effective members of the digitalis series. Now, digitalis is the most valuable heart stimulant known to medicine, but it consists of a mixture of principles and it is one of the most unsatisfactory of drugs to handle, because of the difficulties of securing uniform preparations of it, on whose effects the physician may count with absolute certainty. It is also difficult to secure reliable preparations for hypodermic injections with their advantages of almost instantaneous results. A pure chemical principle with the same action on the heart as digitalis would be free from all of these vital defects and would prove an invaluable addition to our materia medica. With the limited resources in personnel, supplies, etc., our university men have not been able to develop this promising investigation by any large scale preparation, and now a German chemist, with the munificent support of German chemical industries, is moving at top speed to isolate in quantity and commercialize a similar principle found in a species of German toad.

It was doubtless the limitations of research in the medical schools which led to the founding of a con-

siderable number of institutes for medical research; some of these are in connection with universities or hospitals, while others are entirely independent.

Special Institutes for Medical Research in the United States.—The largest and most prominent of these institutes is the *Rockefeller Institute for Medical Research*. The staff of this institute consists of ten "members" with their associates and assistants. Eight of these "members" are occupied with studies on bacteriology, pathology, immunology, serology, general physiology, diseases of animals, experimental surgery, clinical researches on diabetes, heart disease, kidney disease, pneumonia, yellow fever, meningitis, infantile paralysis, etc. In the fall of 1920 announcement was made that during the ensuing winter the following diseases would be made the subject of special study at the institute: acute lobar pneumonia and other acute pulmonary infections, measles, acute rheumatic fever, cardiac disease and nephritis. Two "members" devote their time to chemical work. The activities of the one relate largely to the structural chemistry of nucleic acids, lipoids, and other important components of the body. Under this "member," also, are chemists whose work relates to chemo-therapy; their researches have extended to such compounds as derivatives of hexamethylenetetramine, of certain arsenic acids and of quinine. A number of these derivatives have been tested in other divisions of the institute and in the hospital, for their therapeutic action. The other chemical "member" works in connection with the hospital of the institute, and his work at present relates chiefly to refinements in the methods of blood analysis and other methods of clinical interest. A third "member" of the institute is working on the fundamental

theory of colloids and the application of other physical relations to life phenomena. Part of the excellent work of this institute is in the direction of our chief aims, but the emphasis is rather placed on the pathological and other medical features of the problems than on the direct attack on the problems of medicine by means of a concerted, wholly coöperative effort of leaders in the fundamental sciences of chemistry and physics, in pharmacology and in medicine.

The *Otho S. A. Sprague Memorial Institute*, which is closely affiliated with the University of Chicago, covers in part the same class of problems as does the Rockefeller Institute, but rather more emphasis is placed upon the chemical aspects of medical problems. The Sprague Institute has no buildings of its own, but coöperates "with existing institutions wherever and whenever it seems that medical research can be furthered." In pursuance of this policy it supports work in various laboratories of the University of Chicago and in several hospitals. Among the major problems studied are cancer, diabetes, chronic articular rheumatism, dementia precox, occupational and children's diseases. Among the more strictly chemical studies may be mentioned a series of investigations on the chemistry of the tubercle bacillus; studies on the chemical aspects of diabetes and gout, of immunology, of protein therapy and of the amines obtained from proteins.

Only about half of the members of the staff give full time to the Institute; the others are engaged also in the practice of medicine or in teaching. Excellent as is the work being performed, there is no intensive, concerted attack on problems by any

such group of experts as is contemplated in this report.

The *John McCormick Institute for Infectious Diseases* is also located in Chicago; its problems are chiefly connected with those of infection and immunity.

Other Facilities and Laboratories.—There are a number of other institutes and laboratories in connection with medical schools and hospitals, founded for medical research, such as the *Mayo Foundation,* Rochester, Minn., the *George Williams Hooper Foundation for Medical Research* of the University of California Medical School, the *Nelson Morris Memorial Institute for Medical Research* of the Michael Reese Hospital in Chicago, the *H. K. Cushing Laboratory of Experimental Medicine* at Western Reserve University, the *John Herr Musser Department of Research Medicine* of the University of Pennsylvania, the *Bender Hygienic Laboratory* at Albany, and the *Harriman Research Laboratory* at the Roosevelt Hospital in New York.

Study of Special Diseases.—In addition to the above mentioned laboratories and general institutes for medical research there are a number of institutes, laboratories, funds and foundations for the study of special diseases. Among these may be mentioned the following for the study of *cancer:* The *George Crocker Special Research Fund* at Columbia University, the *Huntington Funds for Cancer Research* at the Memorial Hospital, New York, and at the Harvard Medical School, the *Cancer Laboratory* of the *New York State Department of Health* at Buffalo and the *Laboratory of the Barnard Free Skin and Cancer Hospital* at St. Louis.

There are also a number of foundations for the study of *tuberculosis,* such as the *Henry Phipps*

Institute at Philadelphia, the *Trudeau Foundation for Research and Teaching in Tuberculosis* at Trudeau, N. Y., the *Research Department of the National Jewish Hospital for Consumptives* at Denver, the *Kenneth Dows Fund for the Study of Tuberculosis* at the Johns Hopkins Hospital, etc.

A considerable amount of chemical work is done at some of these foundations, but it relates largely to the applications of chemistry to diagnosis and to problems in bacteriology and pathology, although some work is done on chemo-therapy and at the Mayo Foundation Kendall is doing his important work on thyroxin, a very active compound separated from the thyroid gland and which can replace the latter in therapeutics.

The *Dermatological Research Laboratories* of the Philadelphia Polyclinic have done very important work on the preparation of arsphenamine and on chemo-therapeutic studies with this and other arsenic and also mercury compounds, as well as on metabolism in certain skin diseases.

The laboratories of the *James Buchanan Brady Urological Institute* of the Johns Hopkins Hospital have made studies on new antiseptics of interest in urology.

The *Russell Sage Institute of Pathology*, in affiliation with Bellevue Hospital, New York, is making important calorimetric studies of the metabolism in various diseases.

Lack of Coöperative Attack on Medical Problems.—In none of the many institutions that have been enumerated, important as is their output in research, highly needed as they all are, is provision made for the coöperative attack on problems of medicine by great leaders in the fields of medicine and the fundamental sciences.

Medical Research in United States Government Laboratories.—The money spent annually on chemical work by the *United States Government* runs into the millions. Nearly all of this, however, is for technical or economic purposes or in connection with law enforcement. Only a very small part of it goes for researches in the lines under consideration; in fact, except for some more or less incidental, but very important, work in the Department of Agriculture and work done by the Army and Navy with special reference to military problems, almost the only research work bearing directly upon the health of man is that carried on in the Public Health Service, and especially in the Hygienic Laboratory. In the latter there is a small division of chemistry and also a division of pharmacology in which some chemical work is done. In recent years the chief activities of the division of chemistry have been directed to sanitary engineering; but now there are prospects of some fundamental work on the metabolism of bacteria. The chemical work in the division of pharmacology has been largely in connection with the standards and legal control of drugs, although there has been some work on chemo-therapy and on the relation of chemical structure to physiological action; at present chemical work in connection with tuberculosis is being developed.

Of the present Government laboratories the Hygienic Laboratory would be the best adapted for development into a medium of coöperative research such as that being considered. But judging from the past and present, there seems little probability that this will occur. Congress has never made the positions in this laboratory sufficiently attractive from the standpoint of salaries or of facilities and freedom for work to long retain the services of

chemists of eminence; in the seventeen years of the existence of this laboratory there have been four chiefs of the chemical division and the position has been vacant for about a fourth of the time.

Value of Chemical Work on Leprosy.—The appreciation of chemical work on the part of the medical men of the Public Health Service and an example of its value in public health work were shown by a recent report from the *Service's Leprosy Investigation Station* at Honolulu and Molokai. The Director of this *station*, in discussing leprosy, states that earlier experiments with chaulmoogra oil indicated that there is in this oil "a most valuable curative agent or active principle appealing to chemistry for its isolation, or, at least, identification"; and then relates how, when the coöperation of a chemist was obtained and the ethyl esters of the acids of this oil were prepared and injected into lepers seventy-eight of the latter were cured of the disease. Such a striking demonstration of the value of the coöperation of chemists with physicians can hardly fail to make an impression on Congress, but it seems improbable that any group of chemists in the Government laboratories will be left free from routine or law-enforcing problems sufficiently long to accomplish much fundamental work. Public funds, moreover, are only appropriated for specific purposes and the necessary freedom for work on fundamental principles would therefore be practically impossible in a Government institute.

Medical Research in Manufacturing Establishments.—It is difficult to secure accurate data in regard to research work now in progress or contemplated in *industrial laboratories*, as there is always a natural desire to keep such knowledge from competitors until patents can be applied for or until

the products resulting from the research, if not patentable, are ready for the market. Although a considerable proportion of the drugs now in use have resulted from researches carried on in the laboratories of manufacturing establishments, most of this work has been based upon the results of previous fundamental work in universities or other institutions. Although many pharmaceutical and chemical manufacturers maintain research organizations which have been an important factor in reaching our present stage of progress, no commercial establishment can maintain a staff of specialists in the various branches of science such as would be required to accomplish effective work of the character now required.

Industrial Research of Great Value.—The research work of commercial firms will of necessity be confined mostly to the methods for manufacturing known products and to the discovery of new substances through the application of well-established principles. Researches of this kind are reasonably sure to develop improved medicinal agents of the types already in use, and in this way to secure the financial returns necessary to successful manufacturing operations. Such progress is of great value, as it results in a gradual but steady improvement in medicinal substances and in building up manufacturing facilities and experience so necessary to the complete development of our chemical industry.

Manufacturers Would Assist.—The industries could be very helpful by manufacturing and supplying chemicals required for research purposes and by carrying out operations on a scale not feasible outside of a well-equipped factory. All of the progressive chemical and pharmaceutical manufacturers

would willingly assist in this manner, and a number of firms engaged in the manufacture of dyes and technical chemicals would also be willing to supply chemicals and intermediates to be used in the preparation of medicinal products. On the other hand, research of the character contemplated would be helpful to our chemical industry, as it would stimulate the manufacture of distinctively American medicinal products.

While we have thus in the universities, in research institutes and certain Government laboratories a considerable amount of most important work for the discovery of the cause and prevention of disease, there is not in a single institution that coöperative effort of leaders in the field of organic chemistry, physical chemistry, pharmacology and medicine.

Isolation Bars Progress.—The efforts are isolated. We have in one institute the eminent pathologist with chemical assistance, but lacking the constant full-time coöperation of leaders in synthetic organic chemistry, in physical chemistry, in pharmacology. In another institute a great chemist may be working, but his brother chemist, the leader in physical chemistry, and the great pharmacologist, are lacking. There is thus no single institute in which the whole effort is based on the joint attack on fundamental problems of medicine by leaders in chemistry, physics, pharmacology and medicine.

Foreign Institutes and Laboratories

Medical Research in Germany.—Of the institutes in Germany where the applications of chemistry to the cure of disease are studied, the *Institute for Experimental Therapy* at Frankfort is probably the best known. This Institute was founded in 1899,

in recognition of Ehrlich's services in standardizing diphtheria antitoxin [1] and making it a much more practical remedy. The name "Institute for Serum Investigation" was at first proposed, but Ehrlich requested that no such limitation be placed upon its scope. It was not, however, until 1906, that Ehrlich realized his hopes of being able to work in continuous close coöperation with chemists; this was made possible by the founding and endowment by Frau Speyer of the George Speyer House, an integral part of the Institute, but devoted exclusively to chemical research in connection with biological and especially therapeutic problems.

Ehrlich Calls Chemists.—Ehrlich at once increased the personnel of the Institute (which already included bacteriologists, pathologists and immunologists) by securing not only organic chemists, but physical and biological chemists, protozoölogists, etc. The result of the combined efforts of this group was the discovery of arsphenamine ("606"). Much work was also done upon the chemo-therapy of cancer, sleeping sickness, malaria, etc., and important studies have been made on new classes of germicides (with the hope of finding one which will kill or inhibit bacteria in the human body), on

[1] It is an interesting and apparently unwritten bit of history that Ehrlich was in part led to his important work on diphtheria antitoxin by endeavors to analyze the toxic action of cocaine; it had been reported that the "toxalbumins," ricin and abrin, produced lesions in the liver similar to those he had seen from the "toxophore" group of cocaine; he repeated the experiments with ricin and abrin and discovered that antitoxins are formed which neutralize these toxins in the test tube, and that the strength of the antitoxin may be determined in this way. Up to that time it had been generally believed that antitoxins could neutralize the effects of toxins only indirectly through some obscure action upon living tissues, and a cumbersome and unreliable method of standardizing diphtheria antitoxin was in use. It was largely as a result of these studies of Ehrlich that diphtheria antitoxin became such a trustworthy remedy.

quinine derivatives, the therapeutic value of dyes, etc.

Since Ehrlich's death the work has been continued (with Kolle as director) along both chemotherapeutic and immunological lines, and notwithstanding the greatly reduced budget and personnel as a result of the war, important results have been obtained.

Berlin Boasts Complete Institute.—The success of the Frankfort Institute apparently stimulated the foundation of analogous research institutes in Germany. Thus in 1911 there was founded by private subscription and endowment at Berlin-Lichterfelde another Institute for Experimental Therapeutics (the *Kaiser Wilhelm Institut für experimentelle Therapie*), with Wassermann, a pupil of Ehrlich, as director and Neuberg in charge of bio-chemistry. This is one of the most completely equipped institutes in the world, and is near a similar Institute for Chemistry and also one for Biology and not far from the Pharmaceutical Institute. It was planned, before the war, to found a similar research institute for physiology. One of the subjects to which special attention is devoted is the metabolism of bacteria, which is the fundamental basis for the treatment of bacterial infections.

A Division of Chemo-Therapy.—A division for chemo-therapy, in addition to the already existing division of chemistry, has been added to the *Robert Koch Institute for Infectious Diseases*, at Berlin, and placed under the directorship of Morgenoth, one of Ehrlich's most distinguished pupils and the discoverer of the action of ethylhydrocupreine, a derivative of quinine having a highly specific action on the pneumococcus and of value in treating local infections due to this organism.

It is interesting to recall that in this Institute (which was founded by the Prussian Government for Koch in 1891) a large amount of work was done by Koch, von Behring, Ehrlich, Brieger, and others on the chemical nature of bacterial toxins and antitoxins and in a search for germicides which would destroy bacteria in the body. The discovery of the antitoxins for diphtheria and tetanus diverted the studies toward immunity, but Ehrlich always held to the belief that such germicides would be discovered and after spending nearly ten years in studies on immunity was convinced that the prospects for overcoming most infectious diseases by the use of definite chemical compounds were brighter than those for discovering new antitoxins, etc. Now, after nearly thirty years, Morgenoth has again taken up, in the same institute, these earlier lines of work of Koch and Ehrlich and is obtaining encouraging results.

Elaborate Government Laboratories.—Ample facilities for the study of chemical compounds in connection with the cure of disease have been provided in the comparatively new (about 1907) and most elaborate laboratories of the *Imperial Health Office* at Berlin and Dahlem. Some of the earliest and most important work on the study of arsenic compounds in experimental syphilis and sleeping sickness was done here by Uhlenhuth. This office has chemical, pharmacological, zoölogical, hygienic and bacteriological laboratories.

The Prussian Government, in 1895, established in connection with the University of Marburg an *Institute for Hygiene and Experimental Therapy*, and placed it under the directorship of von Behring. The work of this institute has in recent years dealt largely with processes of immunization to diphtheria and tuberculosis, but a large amount of work on

chemical antiseptics has also been done. Chemical studies played a large part in von Behring's work on the antitoxins; he obtained his first antitoxins by the use of cultures and toxins the virulence of which had been lessened by the action of chemical reagents. In fact, just as Ehrlich was led to some of his most important work on immunity by his pharmacological studies, so von Behring arrived at the conception of "soluble toxins" (which led to the discovery of antitoxins) from his endeavors to explain the toxic action of iodoform and also its beneficial action in the healing of wounds.

There are also in Germany many laboratories and institutes devoted to the study of special diseases in which considerable chemical work, from the standpoint of treatment, is done. Thus important work in chemo-therapy, especially in relation to malaria and sleeping sickness, is being done in the *Institute for Naval and Tropical Diseases* at Hamburg, in which a special Chemical Division for such work has been established.

Institutes for Cancer Study.—The Charité Hospital at Berlin for many years maintained an *Institute for the Study of Cancer;* it was founded originally for the study of the cause of this disease. Then for a number of years the activities were directed toward chemo-therapy; Emil Fischer cooperated in this work and had a large number of new chemical compounds prepared which were tested for possible therapeutic effects. More recently the scope of the work has been enlarged and such problems as the biology of plant tumors have been taken up. There is also an *Institute for the Experimental Study of Cancer* at Heidelberg and a Division for the study of this disease in the Frankfort Institute for Experimental Therapy; in both of

these considerable chemical work, from the standpoint of treatment, has been done.

Much valuable work continues to be done by the University Institutes of Pharmacology, for unlike the situation in this country, all of the German universities have for many years supported large independent departments of pharmacology.[1]

Medical Research in France.—The only noteworthy French institutes for medical and biological research are the *Pasteur Institute* at Paris and the analogous, but smaller, Pasteur Institutes at Lille and Tunis. The Paris Pasteur Institute (founded by public subscription in 1885 for the prevention and treatment of rabies) consists at present of three institutes: bacteriological, serotherapeutic and bio-chemical, each with a number of subdivisions. The bio-chemical institute has divisions of biological chemistry, physical chemistry and "therapeutic chemistry."

A large amount of bio-chemical work has been done, especially by Bertrand and his co-workers, on glucosides, enzymes, the occurrence of manganese, boron, etc., in nature and the effects of certain chemicals upon the biological activities of bacteria. Many physical chemical studies relating to biological problems have been carried on in the division of physical chemistry. In the division of therapeutic chemistry much work has been done on alkaloids, amines, chlorine derivatives, and other compounds

[1] The same was true of the universities of Austria, Hungary, Russia, Sweden, Norway and Switzerland; and Holland has recently established pharmacological institutes at all of the Universities where they were not already present. The leading veterinary schools of Germany, Austria and Hungary also had independent chairs and institutes of pharmacology. In fact, there were about as many real departments of pharmacology in these veterinary schools as there are in the medical schools in the United States at present.

of pharmacological interest; also important work on the relation of chemical structure to physiological action; the chemistry of a number of arsenic and mercury compounds of interest in the treatment of syphilis and sleeping sickness and a long series of studies on local anæsthetics from which the discovery of "stovaine" resulted.

Many of the men at the Pasteur Institute are "part-time" men, holding also teaching or research positions in educational or other institutions. In fact, it is difficult to determine how much of the work mentioned above should be credited to the Institute and how much to other institutions.

Medical Research in England.—Probably the Laboratories in *England* which have done the most coöperative work on the relations of chemistry to physiology and pharmacology are the *Wellcome Physiological* and the *Wellcome Chemical Research Laboratories,* located, respectively, at Herne Hill and Snow Hill, London. These were established in 1894 by H. S. Wellcome, of the firm Burroughs, Wellcome & Co., but the investigations conducted in them have been practically entirely separated from the commercial interests of this firm.

In the physiological laboratory the pharmacologists Dale, Laidlaw, and others and the chemists Barger, Walpole, Ewins, Carr, and others made many important contributions to the relations between drugs and certain parts of the nervous system; the isolation and pharmacological study of active amines from putrid meat, ergot and other sources and the determination of the constitution and the synthesis of some of them; very important studies on anaphylaxis, the pituitary gland, on esters and ethers of choline, etc., as well as many studies of more purely chemical or physiological interest.

This laboratory has also coöperated on a number of problems with the chemists of the Wellcome Chemical Research Laboratory (for example on the synthesis of substances allied to epinephrine) and with the chemists of the Wellcome Works (for example on the relation between chemical constitution and physiological action of large groups of alkaloids and other organic compounds). In the Wellcome Chemical Research Laboratory important work of biological interest was done on many compounds related to atrophine, epinephrine, etc., and chemical examinations of many plants of reputed therapeutic value made; among the latter may be mentioned a study of the fatty acids of chaulmoogra oil, the esters of which are now proving of so much value in the treatment of leprosy.

Many changes in the personnel of these laboratories occurred just before and during the war, and whether the work will be carried on in the future on the same scale seems doubtful.

England to Study Chemo-Medical Problems.—Some of the former members of the physiological laboratory are now inaugurating somewhat similar work in the department of pharmacology and biochemistry of the newly organized *Ministry of Health,* in which plans have been made for the extensive prosecution of studies on the relations of chemistry to biological and medical problems.

Of other laboratories and institutions in England in which studies on the applications of chemistry to biological and medical problems are conducted may be mentioned the *Lister Institute of Preventive Medicine* (founded in 1891 for somewhat the same purposes as the Pasteur Institute), in which, in addition to the work on problems of immunity, serum therapy, etc., some fundamental studies on the action

of antiseptics, and, more recently, a very comprehensive study of the vitamines have been made; the *Liverpool School of Tropical Medicine*, and its allied laboratories, where pioneer work was done on the treatment of sleeping sickness with arsenicals; the *Imperial Cancer Research Fund* and the *Cancer Research Laboratories of the Middlesex Hospital*.

Most of the Universities of England and Scotland have well-equipped departments of pharmacology in which much valuable work is being done.

Medical Research in Japan.—The leading institute for medical research in Japan is the *Kitasato Institute for Infectious Diseases*. This was established as a private foundation in 1892 by Koch's pupil and co-worker Kitasato, and was modeled after the Prussian Institute for Infectious Diseases; it was soon taken over by the Government, but in 1914 was enlarged and became again a private institute. A division of chemo-therapy was added and placed in charge of Hata, the associate of Ehrlich in the discovery of "606."

The Universities of Japan have departments of pharmacology which seem to be at least the equal of those in this country.

CONCLUSION

Every single change of every living organism is unquestionably chemical and physical in its fundamental character, but the organism as a whole is still far beyond the scope of the chemist and physicist. No one has converted lifeless into living

matter without the aid of life itself. We have in life a marvelously organized system for coördinated, highly complex physical and chemical reactions which are in a normal condition largely self-regulating. With all the advances of exact science, it will probably be beyond the power of man to duplicate life's organization, even in its lowest and simplest forms, for many, many generations to come. We still must adhere to the profound advice of Bacon: "Nature is to be commanded only by obeying her."

Every single biological change, in health and in disease, is in turn fundamentally a chemical and physical process, subject to the vigorous, exact laws of chemistry and physics.

Life and Health Demand Science Coöperation.—The problems of life and health, as safeguarded by medicine, are in their very nature so complex that rapid successful advance demands the *coöperative effort of scientists of the highest type,* each a leader in his field and deeply interested in the correlated fields of science, willing to merge his talents and his effort in the common problem for the common good.

A fundamental attack on the problem of the more successful preservation of health and cure of disease demands the coöperative effort of the chemist, the physicist, and those experts in the fields of biology who are most immediately concerned with the scientific study of disease, namely, the pathologist, who studies the changes in the organisms produced by disease, the bacteriologist, student of our chief enemies, the microörganisms or disease germs, and the pharmacologist, who investigates the effects of drugs of all kinds on the organism.

The biologist—pathologist, bacteriologist, or pharmacologist—would be wholly at a loss in a

thoroughgoing effort to chart the seas of disease and health without the aid of the chemist and physicist to study minutely and exhaustively those chemical and physical questions which form the very breath of life.

Chemistry and Physics Needed.—Medical investigators are returning to the universities for the study of more chemistry and more physics. Others are planning to have their sons study chemistry and physics exhaustively before turning to the study of medicine. There are great biologists who have devoted years of study to the fundamental sciences with a great measure of success. These are but evidences of the widespread recognition of the path that promises the greatest measure of progress in medicine.

Coöperative Effort a War Lesson.—But with the tremendous fields covered by each individual science—biology, pathology, bacteriology, pharmacology, physics, organic chemistry, physical chemistry—it is evident that greater advances can be made, more rapidly and more certainly, by the coöperative effort of congenial men. This was the lesson of the war; it must be the lesson of peace. It will fall to the lot, therefore, of the thoroughly trained chemist and the leader in physics, by minute analysis of substance and function, and by the application of the methods of synthesis, to supply to the biologist that exact knowledge of the units and forces from which the complex whole is elaborated, which will ultimately raise medicine from the level of an art to the higher level of an exact science of healing and preservation of health.

America Lacks Coöperative Research.—We have in this country a number of excellent research institutes devoted to medical investigations, with

staffs of the highest calibre. It must be said, however, without fear of contradiction, that there is not a single organization whose purpose is a determined coöperative attack on the problems of disease and health, where intense chemical and physical research goes hand in hand with the medical and biological study of disease. The importance of chemistry and physics has been recognized, but the direction of research is still essentially in the hands of medical men. No one of the scientific groups alone should be entrusted with leadership. All are needed for coping successfully with the complex and formidable problems. Complete coöperation of a staff of experts, peers in every sense, each in his own field, with emphasis on the fundamental, chemical and physical character of the problems, has nowhere been accomplished. Consequently it is proposed that the attack be actually coöperative, from the selection of the problem and the formulation of the plan of work through the whole concentrated effort to grapple with Nature and ultimately to conquer outpost after outpost of the complex world of life.

May the day come when the lesson of the power of coöperative scientific endeavor, so effectively utilized in the Chemical Warfare Service organization, may be applied with equal success to the solution of the problems of disease and health.